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Background Paper

Review of Mass Drug Administration and Primaquine Use

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From evidence to action

Contents

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Acronyms

ACT – Artemisinin Combination Therapy

AFRO – Regional Office for Africa (WHO)

API – Annual Parasite Incidence

CQ – Chloroquine

DOT – Directly Observed Treatment

DPRK – Democratic People's Republic of Korea

EIR – Entomological Inoculation Rate

EMRO – Regional Office for the Eastern Mediterranean (WHO)

EURO – Regional Office for Europe (WHO)

FEMSE – Fast Elimination of Malaria by Source Eradication

G6PD – Glucose-6-Phosphate Dehydrogenase

GMEP – Global Malaria Eradication Programme

IPT – Intermittent Preventive Treatment

IPTi – Intermittent Preventive Treatment to Infants

IPTp – Intermittent Preventive Treatment to Pregnant Women

IRS – Indoor Residual Spraying

ITN – Insecticide Treated Net

MDA – Mass Drug Administration

MPPT – Mass Primaquine Prophylactic Treatment

MSAT – Mass Screen and Treat

PAHO – Regional Office for the Americas (WHO)

PP – Parasite Prevalence

PQ – Primaquine

PYR – Pyrimethamine

RCT – Randomized Control Trial

SEARO – Regional Office for South-East Asia (WHO)

SP – Sulfadoxine-Pyrimethamine

WHO – World Health Organization

WPRO – Regional Office for the Western Pacific (WHO)

Introduction

Mass drug administration (MDA) was a component of many malaria elimination programs during the eradication era. Since then, however, it has been viewed with skepticism due to concerns regarding its efficacy, logistical feasibility, sustainability as a malaria control tool, and fear of accelerating drug resistance. But in light of the availability of transmission-reducing antimalarials, e.g. artemisinin-based combination therapies and primaquine, and the limitations of current diagnostic tools to detect sub-patent infections, the role of MDA as an elimination tool must be reexamined.[1,2]

The empiric use of antimalarial drugs can be generally grouped into four sometimes-overlapping categories: 1) chemoprophylaxis, in which drugs are administered at suppressive doses throughout the defined period; 2) intermittent preventive treatment (IPT), in which a full curative dose of an antimalarial is given to the target population at specified times; 3) direct MDA, in which drugs are administered to the entire population using full therapeutic courses; and 4) indirect MDA, in which drugs are administered through the fortification of salt.[3,4]

Although the World Health Organization (WHO) discouraged the use of MDA in the past, many malaria programs in regions with the most experience in malaria elimination, notably the former USSR and China, have widely implemented MDA both to eliminate malaria and as an epidemic response. Numerous field studies have attempted to interrupt transmission, and while most failed, there are several examples where MDA, in combination with other malaria control measures, had success.

Until recently, a systematic and comprehensive analysis of previous MDA experiences had not been done. However, a Cochrane Review assessing the quantitative effects of malaria MDA documented in published studies was just completed[5] (see Appendix A). The authors found that many MDA trials were not detailed enough to include in their analysis, and the included studies were so heterogeneous that only a limited number of conclusions could be made. In order to maximize the learning from previous experiences of malaria MDA and build upon the knowledge base established through the Cochrane Review, a qualitative study was undertaken. This background paper summarizes the findings from the qualitative exercise, lays out knowledge gaps, and provides recommendations to support the use of MDA for malaria elimination and eradication.

Methods

A comprehensive literature review and key informant interviews were conducted in order to thoroughly document current and past MDA strategies. The literature review included published, unpublished, and grey literature in multiple languages from the past century. Key informants with extensive experience conducting MDA in the field were identified and interviewed, and their protocols and unpublished reports were obtained when possible.

- The literature search originated from the Cochrane Review; search terms and resources used can be found on page 8 in Appendix A. In short, 3,048 studies were identified for screening and 240 were assessed for inclusion (a full list of references can be found in Appendix B). 32 studies (13%) that met stringent inclusion criteria were included in the Cochrane Review, which focused its analysis on quantitative outcomes. In order to gain insight from those papers excluded from the review, this background paper reevaluated the 240 studies using less rigorous exclusion criteria (see below and Appendix C for study exclusion/inclusion process).

Exclusion criteria:

1. Individually randomized studies
2. Studies in which the primary focus was not MDA (e.g. historical program reviews that merely made mention of MDA activities, community surveys done in conjunction with MDA)
3. Studies that were not unique (e.g. multiple phases of the same study published separately)
4. Historical accounts of mass quinine distribution in the early 20th century
5. Studies targeting short-term residents of malaria endemic areas (e.g. military, laborers)
6. Studies treating subgroups in which treatment was given at milestones rather than calendar dates (e.g. intermittent preventive treatment to infants [IPTi] coinciding with the vaccination schedule, or pregnant women [IPTp] coinciding with trimester check-ups)

This resulted in the inclusion of studies that used inadequate treatment doses (chemoprophylaxis), treated subgroups according to calendar dates (seasonal malaria chemoprevention), provided insufficient information on drug regimen, populations involved, or outcome measures, and used a mass screen and treat approach. Including these studies provided valuable information on operational details, including delivery strategies, contextual parameters, and other study features that were not examined in the Cochrane Review. Data from all included studies were systematically extracted by the research team and entered into a Qualtrics (Qualtrics, Provo, UT) database for analysis. In this paper, the term MDA is used in reference to the four types of malaria chemoprevention described in Figure 1 under the *Included* headings.

Figure 1. Types of malaria chemoprevention

	Dose			
	Subtherapeutic		Therapeutic	
Population	*Included*	*Excluded*	*Included*	*Excluded*
Subgroup	Chemoprophylaxis In children	Chemopropylaxis in other groups, such as pregnant women	Seasonal malaria chemoprevention	Intermittent preventive treatment in infants and pregnant women
All	Chemoprophylaxis	Medicated salt	Mass drug administration Mass Primaquine prophylactic treatment	None

- In addition to the studies identified in the Cochrane Review, a search of the WHO archives revealed 30 League of Nations reports published by the Malaria Commission from 1924 to 1932.[6] The reports document the use of MDA in what are now the European (EURO) and Eastern Mediterranean (EMRO) regions of the WHO. These studies were evaluated using the same exclusion criteria listed above, but only if they included the use of an 8-aminoquinoline.

- Key informants were identified through published literature and by recommendations from malaria epidemiologists, control specialists and other stakeholders. Interviews were semi-structured (see interview guide Appendix D). During this process, unpublished reports and grey literature were sought and are included in the findings.

Findings

After applying the exclusion criteria described above, 168 studies assessed in the Cochrane Review were analyzed. To facilitate data extraction, some were broken up into sub-studies; as a result, 181 total studies and sub-studies were reviewed. Only two of the League of Nations reports provided enough details on study procedure, drug regimens, and baseline and outcome data to be considered for analysis. One was determined to be a duplicate of a study already included in the Cochrane Review and excluded, thus bringing the total number of analyzed studies to 182. Of these, 67 (37%) were from the African region (AFRO), 21 (12%) from EMRO, 15 (8%) from EURO, 22 (12%) from Region of the Americas (PAHO), 27 (15%) from South-East Asia Region (SEARO), and 30 (16%) from Western Pacific Region (WPRO). The studies span the past century, with the earliest published in 1913 and the most recent in 2011.

Twelve out of 43 MDA studies (28%) that reported follow-up periods of greater than six months were determined to be successful, with success defined as zero indigenous malaria cases in the target population maintained over six months after the end of drug administration (see Table 1). These studies were carried out between 1936 and 2004 and took place in nine different countries. Six were from WPRO, two from EMRO, two from SEARO (both India), and one from AFRO (highlands of Uganda).

Table 1: Studies that interrupted transmission for over 6 months after the end of MDA

Study Author Country Years	Type and goal of MDA	Drug regimen and duration of intervention	Target population description	Method of delivery	Target population size (coverage %)	Baseline endemicity	Parasite species	Timing relative to transmission season	Additional control measures	Outcomes
Dupoux[7] **Tunisia 1936**	**Mass chemo-prophylaxis:** Reduce morbidity	Premaline (dosage ND) every 10 days for 1 month, then every 14 days for 5 months Total duration: 6 months	All individuals	DOT	27,097 (100%)	High (approximate; numerical PP not reported)	ND	After	None	Transmission interrupted with parasite indices reduced to 0 in some areas
Liu[8] **China 1981-1985**	**Mass treatment:** Outbreak response, elimination	During low transmission season: CQ 1200mg + PQ 180 mg over 8 days During high transmission season: CQ 300 mg + PQ 30 mg twice a month Total duration: 5 years	All individuals	ND	26,369 (100%)	Moderate	ND	Year-round	Bed nets	Transmission interrupted PP reduced to 0.05%
Berberian[9] **Lebanon 1946-1947**	**Mass screening and treatment (MSAT), then mass treatment:** Reduce morbidity	CQ 125-500mg weekly Total duration: 7.5 months	All individuals ≥6 months of age	DOT	93-215 (100%)	Moderate	*P. falciparum* *P. vivax*	During and after	IRS immediately after conclusion of MDA	Case incidence decreased to 0.02/1000 persons/month; cases were suspected relapsed *vivax* infections
Dapeng[10] **China 1985-1994**	**Mass treatment:** Elimination	CQ 1500mg + PQ 90mg for 3 consecutive days Total duration: 10 years	All individuals where incidence was ≥5% in previous season	ND	1,052,170 over 10 years (ND)	Low	*P. falciparum* *P. vivax*	During and outside	IRS Bed nets	*P. falciparum* incidence reduced to 0 and *P. vivax* incidence to 0.05/1000 persons/month Success attributed to vector control interventions
Department of Health Taiwan[11] **Taiwan 1955**	**Mass treatment:** Elimination	CQ 12mg/kg single dose Total duration: 2 months	All individuals (except for infants)	DOT	1,502 (ND)	Low	*P. falciparum* *P. vivax* *P. malariae*	End	IRS	Neither MDA nor IRS alone able to bring PP to 0 Combined interventions led to elimination
De Zulueta[12] **Uganda 1960**	**Mass treatment:** Elimination	CQ 200- 600mg + PYR 16.5-49.5mg two single doses Total duration: 6 months	All individuals ≥3 months	ND	8,000-16,000 (50-100%)	Moderate	*P. falciparum* *P. malariae*	During	IRS	Transmission interrupted

Huehne[13] Malaysia Orang Asli 1961-1963	**Mass treatment:** Elimination	CQ 600mg + 49.5mg PYR monthly dose Total duration: 31 months	All individuals	ND	147 (50-75%)	High	*P. falciparum*	Before and after	IRS	IRS + MDA brought PP to 0; outbreak 13 months after MDA ended was due to imported case
Huehne[13] Malaysia Coastal belt 1961-1963	**Mass treatment:** Elimination	CQ 600mg + 49.5mg PYR approximately every 6 months Total duration: 24 months	All individuals	ND	ND	Moderate to high	*P. falciparum*	During	IRS	MDA ceased after 4 rounds with no transmission; Interruption of transmission attributed to IRS, with MDA hastening progress
Kaneko[14] Vanuatu 1991	**Mass treatment:** Elimination	CQ 600mg + SP 1500mg/75mg + PQ 45mg weekly dose in weeks 1, 5 and 9; CQ 300mg + PQ 45mg weekly dose in weeks 2-4 and 6-8 Total duration: 9 weeks	All individuals (pregnant women CQ only; no PQ for infants <3 months)	DOT	718 (90%)	High	*P. falciparum* *P. vivax* *P. malariae*	Before	Bed nets Larviciding Health education	Malaria eliminated from Aneityum
Lakshmana-charyulu[15] India 1961	**Mass treatment:** Outbreak response, elimination	Two rounds CQ + PYR (dosage ND) Total duration: 4 months	All individuals	ND	30,000-35,000 (80%)	Low (pre-outbreak); high at peak of outbreak	*P. falciparum* *P. vivax*	During	IRS	MDA brought PP close to 0; IRS and surveillance over next 4 years led to elimination
Singh[16] India 1962-1964	**Mass treatment:** Outbreak response, elimination	PQ 15mg daily for 5 days + CQ 600 mg single dose for 4 rounds; first round treated everyone; subsequent rounds targeted only febrile cases and their contacts Total duration: 2 years	All individuals (except for pregnant women, infants and debilitated)	DOT	22,369 over 2 years (avg 76%)	Low	*P. falciparum* *P. vivax*	After	IRS	MDA and IRS combined controlled outbreak and brought PP to 0
Song[17] Cambodia 2003-2004	**Mass treatment:** Elimination	Artemisinin-piperaquine 24-750mg, two doses given at 0 and 24 h (second round one year later in some villages) + PQ 9mg every 10 days for 6 consecutive months Total duration: 6 months – 1 year	All individuals ≥1 year	DOT	2,387- 3,653 (ND)	Low, moderate, and high villages	*P. falciparum* *P. vivax* *P. malariae*	ND	None	PP reduced to 0 in some villages; gametocytemia reduced to 0.6% after 1 year follow up

Note: High endemicity = ≥40% parasite prevalence; moderate endemicity = 5.1-39.9% parasite prevalence; low endemicity = ≤5% parasite prevalence
CQ: chloroquine; DOT: directly observed treatment; IRS: indoor residual spraying; ND: not described; PP: parasite prevalence; PQ: primaquine; PYR: pyrimethamine; SP: sulfadoxine-pyrimethamine

Several reports were obtained from key informants, documenting the implementation of MDA campaigns in the field that have not been published in English language journals[1]. Most were large-scale projects that sought to interrupt transmission using different drug regimens, some in response to epidemics, with varying degrees of success. These are described in more detail in the Study Outcomes section and in Table 2, which summarizes all large-scale MDAs with target populations greater than 100,000. The unpublished reports include campaigns that took place in Nissan (an island in Papua New Guinea) in the 1960s, Afghanistan in the early 1970s, Azerbaijan in the 1970s and 1980s, the Solomon Islands in the late 1980s, Tajikistan in the late 1990s/early 2000s, China in the 1970s and 2000s, and Democratic People's Republic of Korea (DPRK) in the 2000s.

The data extracted from the literature review, League of Nations report, unpublished/grey literature, and qualitative interviews are organized by topic below. The reviewed studies varied considerably in terms of design, rigor, and depth and quality of data, limiting their analysis and comparability. Qualitative data obtained from key informants was therefore essential to gain a more comprehensive understanding of past MDA experiences. Due to the overall paucity of high quality data, equal weight is given to each data source.

Study objectives and design

Study objectives were classified as either 1) morbidity reduction; 2) elimination/interruption of transmission; or 3) outbreak response. Many of the 182 studies reviewed did not clearly define their objectives; however, the vast majority of objectives were directed at morbidity reduction. About one-third of the studies aimed to eliminate or interrupt transmission, and a small portion were specific to outbreak settings. Most of the unpublished work shared by key informants sought to interrupt transmission in areas of varying endemicity or in post-eradication era epidemic settings. Regardless of their personal experiences, multiple key informants stated that MDA can be used to achieve all three objectives (1-3 above) as long as the interventions are contextual, carefully planned and appropriately implemented.

Most published studies did not have a rigorous design: 27% were descriptive, 52% were before and after studies, 17% were non-randomized control trials (non-RCT), and only 4% were RCT/cluster RCT. While many were described by the authors as MDA, the majority did not meet the definition used in the Cochrane Review (drugs administered to the entire population using full therapeutic courses) and instead should be considered chemoprophylaxis due to their use of a suppressive dose of drugs. Only 42 studies (23%) involved MDA with therapeutic doses, while 107 (59%) were chemoprophylaxis, 13 (7%) were mass screen and treat (MSAT), and 20 studies did not adequately describe the drug regimen. Of the 12 successful studies, 11 used treatment doses. One small study[9] of uncertain quality was initiated using a MSAT approach; however, the entire population regardless of infection status was shifted into the presumptive treatment group one-third of the way into the study period. Apart from this study, no other MSAT studies showed sustained success (of note, this background paper does not specifically address MSAT; MSAT was not included in the literature search nor were questions related to MSAT included in the interviews or searches for grey and unpublished reports). All unpublished work documented the administration of therapeutic doses.

Duration of intervention for both published and unpublished studies was highly variable, ranging from a single day to ten years. The majority of the studies (63%) lasted nine months or less. Half of the 12 successful studies were of a shorter duration, lasting two to seven months, while the other half ranged from one to ten years.

[1] When this review began, the paper documenting MDA in Jiangsu Province, China in the 1970s and 2000s had not yet been submitted for publication; it was published in *Malaria Journal* on November 1, 2013.[18]

Contextual parameters - endemicity, seasonality, target population

Level of **endemicity** was difficult to capture consistently from the published studies, as many provided baseline parasite prevalence or incidence only for subgroups (e.g. infants, school-aged children) and others provided no baseline data at all. To the degree possible, endemicities were grouped into the same categories as those in the Cochrane Review: low (≤5%), moderate (5.1-39.9%), and high (≥40%)[19] using baseline malaria prevalence or baseline spleen index. For the studies that reported these indices, 43 (24%) were undertaken in what was classified as a high endemic area, 56 (31%) in a moderate endemic area, and 15 (8%) in a low endemic area. Eleven studies targeted groups in both moderate and high endemic areas, and one study was conducted among groups in both moderate and low endemic areas. Of the studies that conducted successful MDA, eight took place in moderate and high endemic areas, three were conducted in low endemic areas and one was conducted during an outbreak in a usually low endemic area (see Table 1). Most of the unpublished work fell into the moderate/low endemicity category, although some of the campaigns were implemented in high transmission areas with up to 95% baseline prevalence. Key informants agreed that MDA is quite effective in rapidly reducing very high transmission to lower levels, although maintaining transmission at this lower level was noted to be a challenge. Key informants generally thought that low endemic settings were most appropriate for the goal of elimination.

Although some of the published studies did not provide **seasonality** information, the majority reported interventions that took place during the transmission season. Their objectives were to control outbreaks, reduce morbidity during the transmission season, or test the efficacy of specific drugs on malaria transmission. Many MDA interventions were successful at considerably decreasing malaria incidence and prevalence during the intervention period; however these indices typically increased a few weeks to a few months after the interventions ended. The majority of the published studies were conducted during the transmission season. Of the 12 successful studies, 11 reported seasonality: four were conducted during transmission, four during the off season, and three spanned seasons (see Table 1).

Key informant input on seasonality varied. Two informants stated that the timing of the intervention in relation to the malaria season depends on study objectives and drug regimen. For example, chemoprophylaxis for reduction of morbidity can be implemented year round. Another consideration is logistical: conducting fieldwork and accessing target populations is easier during the dry season than during the rainy season, which often coincides with malaria transmission. Key informants strongly believed that when seeking to interrupt transmission in areas with clear, relatively predictable seasonality, MDA is best conducted just prior to the transmission season when malaria incidence is at its lowest point and the target population is most stable.

The **populations** targeted in published studies varied considerably, from small villages of less than 100 people to the entire population of a country with nearly two million inhabitants.[20] Most studies targeted populations in the hundreds or thousands. Table 2 summarizes the MDA reports (published and unpublished) that were conducted on a large scale, covering over 100,000 people. The populations' ages vary across the studies. Just over half of the studies included all age groups. When excluded groups were described, they were most often infants (less than one year), pregnant women, patients recently treated for malaria, and people with chronic illness. All of the successful studies targeted entire populations of varying size (with one exception[16], in which only febrile cases and their immediate contacts were treated in subsequent rounds, after an initial round of treating the entire population), and if exclusions were noted they were the same groups as described above. The MDA work discussed with key informants was of a much larger scale, with targeted populations in the tens and hundreds of thousands and reaching up to 28 million per annum in Jiangsu, China, and included all ages. Excluded groups, when addressed, were found to be the same, although in some very recent MDA campaigns pregnant women and young children were included due to a drug regimen (specifically, a very low-dose primaquine[21]) that was considered safe by the study team.

Table 2: Large scale MDAs*

Study Author Country Years	Type and goal of MDA	Drug regimen and duration of intervention	Target population description	Method of delivery	Target population size (coverage %)	Baseline endemicity	Parasite species	Timing relative to transmission season	Additional control measures	Outcomes
Han[22] Republic of Korea 1997-2005	**Mass chemo-prophylaxis:** Control	CQ 300mg weekly for active duty soldiers; PQ 14mg/day for 14 days for soldiers upon retirement Total duration: 9 years	Active and retired soldiers	ND	985,282 over 9 years (ND)	Low	*P. vivax*	Year-round	IRS Bed nets	Mass chemoprophylaxis reduced incidence to 0.08/1000 persons/month among soldiers
Joncour[23] Madagascar 1949-1955	**Mass chemo-prophylaxis:** Control and elimination	CQ 300mg/week Total duration: 2 years	All individuals age 0-13	DOT	760,000 (100%)	High	*P. falciparum* *P. vivax* *P. malariae*	Year-round	IRS Larviciding	Chemoprophylaxis decreased morbidity and mortality; PP was 10-35% among treated population and higher among untreated
Ossi[24] Iraq 1963	**Mass chemo-prophylaxis:** Outbreak control and Elimination	CQ 450mg + PYR 50mg twice per month Total duration: 4 months	All individuals	ND	250,000 (80%)	High	*P. falciparum* *P. vivax*	During	IRS Active case detection	MDA decreased morbidity but unsuccessful at interrupting autumn transmission
Kondrashin Azerbaijan 1971-1975 (unpublished)	**Mass primaquine prophylactic treatment (MPPT):** Elimination	PQ 15mg daily for 14 days Total duration: 5 years	All individuals (except for infants, pregnant women, chronically ill)	DOT	10,587-106,555 (87-93%)	Low (high during epidemic)	*P. vivax*	Outside	None	MPPT effectively controlled epidemic and decreased PP to 0.7% at end of intervention; PP maintained for several years with only residual active foci
Kondrashin DPRK 2002-2007 (unpublished)	**Mass primaquine prophylactic treatment (MPPT):** Control	PQ 15mg daily for 14 days Total duration: 6 years	All individuals ≥5 years (except pregnant women)	DOT	378,366-4,904,261 (94-98%)	Low (high during epidemic)	*P. vivax*	Before	None	MPPT decreased PP considerably but failed to interrupt transmission
Aliev[25] Tajikistan 1998-1999	**Mass treatment:** Outbreak control and elimination	PQ (dosage and regimen ND) Total duration: 2 years	All individuals	DOT	257,200-421,000 (ND)	Low (high during epidemic)	ND	Before	IRS Larviciding	MDA reduced incidence to 0.56/1000 persons/month but failed to interrupt transmission

Dapeng[10] **China 1985-1994**	**Mass treatment:** Elimination	CQ 1500mg + PQ 90mg for 3 consecutive days Total duration: 10 years	All individuals where incidence was ≥5% in previous season	ND	1,052,170 over 10 years (ND)	Low	*P. falciparum* *P. vivax*	During and outside	IRS Bed nets	*P. falciparum* incidence reduced to 0 and *P. vivax* incidence to 0.05/1000 persons/month Success attributed to vector control interventions
Dola[26] **Zanzibar 1968**	**Mass treatment:** Elimination	CQ 300mg + camoquin 300mg + PQ 30mg every two months Total duration: ND	All individuals	ND	124,065 (84%)	Low	*P. falciparum*	Before	None	MDA was ineffective: incidence increased to 10.5/1000 persons/month vs pre-intervention level of 9.7/1000 persons/month
Gabaldon[27] **Venezuela 1957-1958**	**Mass treatment:** Elimination	PYR 50mg weekly Total duration: 24 weeks	All individuals ≥ 1 month	DOT	111,995 (ND)	Low	*P. vivax*	During	IRS Community participation incentives	MDA interrupted transmission, brought PP to 0% but failed to cure all *vivax* infections; transmission resumed after relapses occurred
Garfield[20] **Nicaragua 1981-1982**	**Mass treatment:** Control and elimination	CQ 350-1500mg + PQ 10-45mg over 3 days Total duration: 3 days	All individuals ≥ 1 year	ND	1,900,000 (80%)	Low to moderate	*P. falciparum* *P. vivax*	Beginning	Larviciding, vector control, community education	Incidence of *P. falciparum* declined for 7 months and *P. vivax* declined for 4 months; both then returned to pre-intervention levels
Hsiang[18] **Jiangsu 1973-1983**	**Seasonal mass treatment:** Control of epidemic	1973-1976: PQ 30mg daily for 4 days + PYR 50mg daily for 2 days Total duration: 4 years 1977-1983: PQ 22.5mg + PYR 12.5mg daily for 8 days Total duration: 7 years	1973-1976: All individuals in rural counties 1977-1983: All index cases from previous year and their contacts	DOT	1973-1976: 13,389,482 - 27,974,966 (ND) 1977-1983: 4,446,687 - 16,534,356 (ND)	Low (high during epidemic)	*P. vivax* Minimal *P. falciparum*	1973-1976: Before/ beginning 1977-1983: During	Bed nets (very low coverage), intermittent chemo-prophylaxis	MDA was effective at decreasing parasite reservoir, but did not interrupt transmission API dropped from 113.6 in 1973 to 2.1 in 1983
Hsiang[18] **Jiangsu 2000-2009**	**Focal mass treatment:** Control of epidemic	CQ 400mg daily for 3 days + PQ 22.5mg daily for 8 days Total duration: 10 years	Index cases of past 1-2 years and all contacts (excluded <3 years, pregnant, seriously ill)	DOT	1,863,399-1,926,183 (60-98%)	Low	*P. vivax*	Before	Bed nets (0-8% coverage) IRS (not in all counties)	Targeted MDA was effective in decreasing API to 0 in some areas, but transmission was not interrupted

*Large-scale defined as target populations > 100,000 persons

Note: High endemicity = ≥40% parasite prevalence; moderate endemicity = 5.1-39.9% parasite prevalence; low endemicity = ≤5% parasite prevalence

API: annual parasite index; CQ: chloroquine; DOT: directly observed treatment; IRS: indoor residual spraying; ND: not described; MPPT: mass primaquine prophylactic treatment; PP: parasite prevalence; PQ: primaquine; PYR: pyrimethamine

Outcome measures

Of all outcome measures reported, parasite prevalence was the most common (22% of total), followed by gametocyte prevalence (11.2%) and incidence (case or parasite - 10.1%). Few studies looked at entomological measures such as sporozoite rate or entomological inoculation rate (EIR).

Drug regimens

Drug regimens were diverse, and varied depending on location and timeframe of the study as well as biological concerns including glucose-6-phosphate dehydrogenase (G6PD) deficiency prevalence and drug resistance. Nearly half of the published studies used monotherapy; of those, chloroquine was the most common drug of choice (28%), followed by proguanil (18%) and pyrimethamine (14%). The most frequent combination therapies were chloroquine + primaquine (22%), chloroquine + pyrimethamine (14%), and mepacrine + plasmoquine (11%). 8-aminoquinolines were included in 70 of the studies (38% of total), five of which were monotherapies with either plasmoquine or primaquine. A selection of primaquine-containing regimens is shown in Table 3. Of the 12 successful studies, six included 8-aminoquinolines in combination with other drugs. Two used chloroquine and three combined chloroquine and pyrimethamine. Drug regimens documented in unpublished reports were equally diverse, including primaquine monotherapy, artemisinin derivatives, and various combinations with and without primaquine. Drug dosages and schedules across all MDA studies and programmatic campaigns, published and unpublished, ranged from a single treatment dose given one time to weekly chemoprophylactic doses given over the course of several years.

Table 3: Examples of primaquine-containing MDA drug regimens

MDA Strategy	Drug regimen	G6PD considerations	Adverse events	Outcome	Reference*
Primaquine to target *P. vivax* malaria					
Mass primaquine prophylactic treatment (MPPT)	**Total PQ dose = 210 mg** 15 mg PQ given as directly observed treatment (DOT) daily for 14 days in seasonal settings, either before or after transmission season	G6PD-deficient patients included with close monitoring	Severe side effects related to G6PD deficiency (i.e. red or black urine) did not exceed 1%; minor side effects did not exceed 4%	Considerably reduced case load of *vivax* malaria where alternate forms of malaria control were unavailable	Anatoly Kondrashin: unpublished review of Azerbaijan, Afghanistan, Tajikistan, and Democratic People's Republic of Korea, 1970s-2000s
Nissan Method	**Total PQ dose = 360 – 720 mg** 45-60 mg PQ given weekly for 8-12 weeks, administered as DOT by local residents	Nissan: 30% prevalence of G6PD deficiency (GdA^{-1});G6PD-deficient patients included	Hemoglobin levels in G6PDd checked weekly; weeks 1 and 2 did not drop below 2 g%, rising by week 3; at end of 8 weeks, about 1 g% higher than start of MDA	Pf eliminated completely from Nissan; Pv reduced to low level but not eliminated due to presence of PQ-tolerant Chesson-like strains	Karl Rieckmann: personal account of Nissan experience in early 1960s
	Total PQ dose = 360 mg CQ 600 mg + SP 1500mg/75mg + PQ 45mg once a week in weeks 1, 5 and 9; CQ 300mg + PQ 45mg once a week in weeks 2-4 and 6-8	G6PD-deficiency not detected on Aneityum	None reported	Sustained interruption of malaria transmission	Kaneko 2000[14] Vanuatu
Chinese Method	**Total PQ dose = 180 mg** PQ 22.5 mg daily for 8 days and PYR 50 mg daily for 2 days administered to entire villages in the spring, prior to transmission season	G6PD-deficient patients included	Not systematically monitored; 49 cases of acute hemolysis reported in five studies that identified severe adverse events from G6PDd patients	Seasonal MDA administered to almost 30 million people, malaria incidence decreased by 56.7% 1973-76, and by 12.4% 1976-83	Hsiang 2013[18] Jiangsu China, 1973-1983

	Total PQ dose = 180 mg CQ 400 mg daily for 3 days + PQ 22.5 mg daily for 8 days, targeted to household members and neighbors of index cases in the spring	G6PD-deficient patients included	5 subjects in 2003 and 2 in 2007; some experienced hemolysis	Malaria incidence decreased by 14%-43.7% in the two counties where MDA was conducted	Hsiang 2013[18] Jiangsu China, 2000 - 2009
	Total PQ dose = 180 mg During low transmission season: CQ 1200mg total + PQ 180 mg total over 8 days; during high transmission season: CQ 300 mg + PQ 30mg twice per month	G6PD-deficient patients included	None reported	Incidence of *vivax* malaria decreased and parasite prevalence maintained at 0% for three years of post-MDA follow-up	Liu 1986[8] China
Singh Method	**Total PQ dose = 75 mg** PQ 15mg/day for 5 days + CQ 600 mg single dose for 4 rounds; first round treated everyone; subsequent rounds targeted only febrile cases and their contacts	G6PD-deficient patients included	None reported	*Vivax* transmission suppressed during study period; incidence decreased from 0.98 to 0.006 cases / 1000 persons/ month, maintained over 1-year follow-up	Singh 1968[16] India
Primaquine to target *P. falciparum* gametocytes					
Fast Elimination of Malaria by Source Eradication (FEMSE) Method	**Total PQ dose = 108 mg** 125 mg of artemisinin + 750 mg piperaquine daily for 2 days, monthly for 2 months + PQ 9 mg every 10 days for 4 months	G6PD-deficient patients included	None reported	Parasite prevalence rate reduced from 21.6% to 0.86% after 18 months	Li 2007, unpublished study in Comoros
	Total PQ dose = 162 mg 125 mg of artemisinin +750 mg piperaquine daily for 2 days + PQ 9 mg every 10 days for 6 months	G6PD-deficient patients included	None reported	Parasite prevalence rate reduced from 52.3% to 2.6% after 3 years	Song 2010[17] Cambodia
Targeted Chemo-Elimination Method	**Total PQ dose = 45 mg** 40 mg of dihydroartemisinin + 320 mg piperaquine daily as DOT for 3 days + PQ 0.25 mg/kg on day 1; regimen given monthly for three months	G6PD-deficient patients included	Results not yet available	Results not yet available	Mahidol-Oxford Research Unit Protocol
Sulfadoxine pyrimethamine + primaquine method	**Total PQ dose = 60 mg** SP 1430-70 mg + PQ 30 mg once per month for 2 months	G6PD-deficient patients included	None reported	*P. falciparum* prevalence temporarily decreased for 2 months after intervention; *P. vivax* prevalence did not change	Hii 1987[28] Malaysia
	Total PQ dose = 84-120 mg Sulfadoxine 25-30 mg/kg + pyrimethamine 1.25-1.5 mg/kg single dose + PQ 0.7-1.0 mg/kg once per week for 2 weeks.	G6PD-deficient patients included	None reported	No difference between "control" and intervention group since control group was treated a few months after the intervention group	Doi 1989[29] Indonesia

*All studies published unless otherwise noted

Emergence of drug resistance was observed or suspected in 16 of the 182 published studies (9%), nearly all of which involved monotherapy. Seven studies based in Africa documented resistance to pyrimethamine, three studies described resistance to proguanil in South East Asia, and two involved chloroquine resistance in Papua New Guinea and Pakistan. Three additional studies documented pyrimethamine or chloroquine resistance in their respective areas, but treatment failures were avoided through the use of combination drug regimens. All of the MDA campaigns described in unpublished literature involved combination therapies, other than primaquine monotherapy, and resistance was not reported. Key informants currently working in the Greater Mekong subregion where artemisinin resistance has been documented[30–32] emphasized the importance of rapidly interrupting transmission within targeted Mekong border populations before it spreads beyond the area of concern. MDA drug regimens in these areas involve artemisinin combination therapies (ACTs) + primaquine.

Only five published studies that included 8-aminoquinolines documented the prevalence of G6PD deficiency in the target population (ranging from 2.1% to 17.1%), all of which were published since 1989. G6PD deficiency was a greater consideration in the unpublished work obtained from and discussed with key informants, some of which dated back to the 1960s. Deficiency prevalence was obtained prior to the onset of interventions and patients were monitored closely for hemolysis and other adverse events throughout drug administration. In the event that patients did experience hemolysis, 8-aminoquinoline was discontinued and in China and DPRK they were excluded from future treatments. Alternatively, in Azerbaijan and Afghanistan, a modified drug regimen was implemented in which the standard 14-day course of primaquine treatment was interrupted and drugs were not given on Days 5-7, then were resumed on Day 8. Because this intermittent schedule was thought to disrupt the hemolytic effects of the drug, it was deemed safe for populations with high prevalence of G6PD deficiency.[33] Regardless of drug regimen, no deaths were documented in any of the unpublished work; patients recovered with routine supportive care and no long-term hospitalization or blood transfusions were necessary. Key informants noted that directly observed treatment (DOT) is essential for monitoring and quickly identifying potential hemolysis cases, and that medical interventions, including blood transfusion, should be readily accessible.

Key informants firmly believed that inclusion of an 8-aminoquinoline in the drug regimen, either primaquine or tafenoquine, was essential for clearing gametocytes and hypnozoites and eliminating the last reservoirs of infection. However, one key informant expressed concern that there is still no published evidence that these drugs interrupt transmission at the community level. Most key informants believed that combination therapy using ACTs plus a single round of low-dose primaquine to avoid G6PD deficiency complications is the best regimen for elimination in *P. falciparum* endemic areas, in contrast to the multiple rounds of primaquine necessary for *P. vivax* elimination. The longer action of tafenoquine was cited by one key informant as an advantage over primaquine, although another believes duration of action is not a significant issue in very low transmission settings and that primaquine is equally effective for *P. falciparum* elimination. In a departure from the ACTs + 8-aminoquinoline consensus, one key informant stated that a multi-day drug combination is too complicated and increases the likelihood that the intervention will fail due to low adherence. Lastly, two key informants mentioned the role of alternative drugs, including ivermectin and methylene blue, and their potential for use in MDA regimens after further research has been done.

Co-Interventions

Co-interventions were deployed in 86 of the 182 published studies (47%). Of these, 65% conducted IRS, primarily using DDT, 33% conducted chemical or biological larval control, 23% carried out environmental management (e.g. vegetation clearing, waterway construction), and 16% distributed bed nets, treated or untreated. Over one-third of the studies implemented multiple co-interventions. Other co-interventions described less frequently included MDA for other diseases, health education, and community surveillance. Ten of the 12 successful studies implemented co-interventions: eight used IRS, three used insecticide treated nets

(ITNs), and two used multiple measures. In interviews, key informants agreed that vector control is essential and should be used prior to commencement of MDA in order to bring transmission down to very low levels. IRS and net distribution were the most frequently cited co-interventions, but the use of transmission-blocking vaccines was mentioned as well. One key informant questioned the role of traditional vector control methods in areas with negligible transmission but high prevalence of asymptomatic, submicroscopic infections, stating that in these settings, preferred co-interventions are strong surveillance and early diagnosis and treatment of imported cases. Two key informants addressed the importance of understanding local vector bionomics when planning co-interventions.

Delivery methods and community engagement

The published studies did not thoroughly or consistently explain their **delivery methods**, but those that did used a wide range of approaches. 58% involved DOT, while 4% did not and the remaining 38% were not described. Of the 12 successful studies that reported the method of drug delivery, six were DOT. Of the DOT studies, drug distribution and observation was performed by community volunteers, local health workers, study authors and/or external organizations. Population censuses and the mobilization of local workers to monitor the movement of people in and out of a study area were employed in some studies. One study[27] described the use of incentives for community participation and adherence to the full MDA regimen, specifically lottery tickets for prizes (sewing machines, bicycles, etc). Six of the successful studies utilized DOT with trained volunteers or the study authors themselves, while delivery methods in the five others were not described.

Different types of **community engagement** were described in the successful studies as well, namely, working with community leaders and elders to ensure cooperation, extensive health education and outreach, and active participation through the formation of volunteer malaria teams. Two study authors specifically noted that strong community participation was crucial for success. According to several key informants, DOT and engagement with the community are vital for the success of MDA. While it may not always be logistically feasible, key informants stated that house-to-house visits are preferred over a centralized distribution location in order to ensure high coverage. Local health workers or volunteers should be utilized for drug distribution since they understand the environment and local customs, and will garner more trust and acceptance among their peers. In addition to extensive outreach and education efforts among local leaders and the larger community, one key informant emphasized the importance of linking participation in MDA with tangible benefits (e.g. child survival, increased productivity and income) when engaging with the target population. In areas with low transmission, another key informant recommended working with older members of the community who may remember when malaria was more prevalent and be more invested in preventing its return.

Study outcomes

Many of the published studies were deemed successful by the authors in achieving their stated objectives, yet for the purposes of this background paper, only 12 met a definition of success that will be most applicable to malaria elimination settings (zero indigenous malaria cases in the target population maintained for at least six months after the end of drug administration). The majority of the studies (63%) had a follow-up period of less than six months, preventing an assessment of the interventions' long-term effects on transmission. Many studies were able to reduce parasite prevalence in the target population, but either were not able to reach zero or prevalence went back up shortly after the drug administration was ceased, a finding echoed in the Cochrane Review.[5]

The primary factors for a successful MDA campaign mentioned almost universally by key informants were: achieving at least 80% coverage of the target population with drug administration based on mathematical modeling[34] (some cited 90% coverage as the minimum necessary), DOT, short-term interventions, high coverage

of vector control interventions, and the use of 8-aminoquinolines. Among the published studies, coverage and adherence outcomes were either not consistently measured or simply were not reported; only 51% of the studies documented coverage achieved, and 28% addressed adherence. 74 of the published studies (41%) reported achievement of >80% coverage of the targeted population, 77% of which involved DOT. An additional 19 studies reached 60-80% coverage, with over half using DOT. DOT was not a guarantee of high coverage; at least 12% of the published studies that involved DOT were not able to achieve 80% coverage. It is important to note that in some of the studies, these measures were described using verbal approximations (e.g. "nearly 100%"[29]), and not hard numbers.

Of the unpublished work, the campaign in the Solomon Islands is a prime example of the importance of community engagement to achieve high coverage. The project targeted a population of around 30,000 in the capital city and was thoroughly planned, well-staffed with local workers, and involved exhaustive community outreach to ensure participation, yet coverage was only 67% due to refusal of the targeted population to take drugs when they were not ill. The 3-day drug regimen further contributed to lack of participation. In comparison, the MDA carried out in Nissan was notable for achieving nearly 100% coverage, attributed to a high degree of community cooperation and a strong health infrastructure that facilitated intense screening of all arrivals to the island. Strong engagement with the community also allowed for rigorous monitoring of adverse events; G6PD deficiency prevalence on Nissan was 30%, but high weekly doses of primaquine did not cause any significant hemolytic effects.

The study documenting MDA carried out in Jiangsu Province, China in the 1970s[18] describes the use of primaquine to interrupt *P. vivax* transmission on a massive scale. *P. falciparum* had nearly been eliminated in Jiangsu, but *P. vivax* epidemics persisted during this period. Entire counties, nearly 30 million people in total, were given directly observed seasonal 'spring treatment' by teams of community health workers and local public health officers prior to the onset of the transmission season, largely in the absence of vector control measures. In later years, a stratified approach was used, in which MDA was targeted to index cases from the previous year and their immediate contacts; this method allowed for improved targeting, reduced worker burden, and greater compliance. Despite the enormous scope of primaquine distribution, the incidence of severe adverse events was negligible and no deaths occurred, according to available records. After ten years, annual parasite index (API) of *P. vivax* in Jiangsu Province dropped from 113.6 to 2.1 per 1,000 population. This experience demonstrates that with ample, well-organized human resources and a DOT delivery strategy, MDA can be implemented on a large scale with success.

The vital role of primaquine in controlling *P. vivax* epidemics is further illustrated in a series of unpublished accounts of MDA in Afghanistan, Azerbaijan, DPRK, and Tajikistan. In these countries, MDA consisted of 14-day courses of primaquine as monotherapy, and the approach was called mass primaquine prophylactic treatment (MPPT). Intermittent MPPT was implemented in Afghanistan and Azerbaijan to prevent hemolytic effects arising from G6PD deficiency, and in all areas adverse events were closely monitored. As in Jiangsu Province, safety issues were rare: across all locations and years, less than 4% of nearly 9 million people treated experienced adverse events, with no blood transfusions reported. In contrast with the Jiangsu account, vector control interventions were considered key to the success of MPPT. However, in Azerbaijan and DPRK a lack of resources led to implementation of MPPT in the absence of vector control, and in Afghanistan and Tajikistan, routine vector control activities were believed to be of poor quality and of limited efficacy. Despite these problems, considerable case reductions and interruption of *P. vivax* epidemics were seen in Afghanistan, Azerbaijan and DPRK, all of which were able to achieve drug coverage of over 90% in populations ranging from 24,000 to 500,000. In Tajikistan, the effects of MPPT were not as pronounced and this was attributed to the fact that population coverage never exceeded 80%. In all locations, obtaining support of local authorities and cooperation

of communities was noted as important for ensuring good coverage and efficiency of drug distribution, as was the use of DOT by teams of primaquine distributors that each served 200-250 people.

Limitations

While the research conducted for this background paper was comprehensive, significant limitations exist. The high variability of study methods and settings as well as the poor quality of data derived from the published literature pose major difficulties for analysis and the drawing of firm, generalizable conclusions based on study results. Over three-fourths of the studies document work done prior to 1970, thus much of this historical expertise is no longer accessible.

Combining the many and somewhat disparate forms of MDA (see Figure 1) into one review may have introduced bias and weakened our findings. For example, the majority of studies documented chemoprophylaxis interventions which involved frequent dosing and were carried out mainly during the malaria transmission season. There were a limited number of transmission-interrupting studies which had fewer rounds of drug delivery and most often occurred during the low transmission season. This bias may have affected our overall conclusions on effect and success of the various forms of MDA. However, the more selective Cochrane Review supports the findings of this review, and by including a wider variety of studies along with key informant input, a broader assessment of factors such as delivery, size of target population, and effects of endemicity could be carried out.

Key informants provided valuable insights based on decades of institutional knowledge and personal experience with MDA, however, this input cannot be treated in the same manner as data derived from a rigorous published study. In addition, not everyone who has experience with MDA was interviewed and the search for unpublished work was not exhaustive, introducing reporting bias to these findings.

Finally, the definition of success used to evaluate the 182 published studies is more applicable to *P. falciparum* than *P. vivax*. The six-month transmission-free period is not sufficient for assessing clearance of hypnozoites, the dormant liver stage of *P. vivax.*

Discussion and conclusions

This extensive review of published, unpublished and grey literature on the topic of malaria chemoprevention has revealed some important learning points that support MDA as a possible intervention that previous, more restricted reviews were unable to do. The learning points support recommendations and highlight important gaps in knowledge that need to be addressed in order to move toward broader implementation.

Learning points

1. **Mass drug administration has been used in large-scale interventions for malaria control, elimination and in response to outbreaks.**
   In this review we found 12 reports of malaria MDA for both *Plasmodium falciparum* and *vivax* used in populations over 100,000, including reports in China that targeted nearly 30 million people (see Table 2).

2. **Mass drug administration and mass chemoprophylaxis are successful at reducing parasite prevalence, but once stopped, there is a tendency for malaria to return to previous transmission levels, particularly in high transmission settings.**
   Supporting previous reviews, including the Cochrane Review, our analysis found that in the majority of cases, MDA and mass chemoprophylaxis reduced parasite prevalence (or other measures of

transmission) only temporarily. Shortly after drug administration concluded, transmission returned to pre-intervention levels, even when combined with vector control and involving an 8-aminoquinoline.

3. Select mass drug administration programs have been successful.

In this review we found 12 published studies that documented sustained benefit from MDA out of 43 studies that reported follow up beyond 6 months after the intervention period (see Table 1). In addition, we discussed unpublished reports that described successes in program-implemented MDA (see Table 2 and text). These published studies and unpublished reports are of varying quality; results cannot be assured nor can causality be attributed to MDA in most settings. However, the fact that these interventions took place and to the scale and degree of success reported is notable and worthy of consideration. Particular learning points are below:

a. Endemicity

Only 13% of published studies that indicated a baseline endemicity took place in low endemic settings, while in the case of program implemented MDA documented in unpublished reports and discussed with key informants, 83% took place in low endemic settings. The published studies may have taken place in higher endemic settings so as to be more likely to measure an outcome[35] and because MDA was a recommended strategy during the Global Malaria Eradication Programme (GMEP) era. As a result, there is a bias toward reports from moderate and high endemic settings. Conversely, because of our selection of key informants, most of whom have carried out programmatic MDA, there may be a bias toward low endemic settings. Nevertheless, it is apparent that MDA has been thought to be more successful in low endemic settings as compared to high or moderate settings. In addition, the infrastructure and human resources needed to deliver MDA are more likely to be available and more readily deployed in low endemic settings where infections are more clustered and countries tend to be better resourced.

b. *P. vivax*

Although the Cochrane Review noted that MDA had a larger impact on *P. falciparum* than *P. vivax*, there is strong evidence presented here for the use of MDA in the elimination of *P. vivax* in seasonal settings. Programs involving multi-day regimens of primaquine through DOT, with or without vector control, resulted in decreased prevalence of malaria and interruption of transmission when drug coverage was high.

c. Small-scale MDA in isolated settings with limited importation risk

Malaria was successfully eliminated from Aneityum (Vanuatu), Lanyu (Taiwan), and Nissan (Papua New Guinea), small island settings where ports of entry were controlled and population movement was closely monitored. Similar success was seen in village settings in Cambodia[17], Lebanon[9], and Malaysia[13] that were relatively isolated, geographically.

d. MDA in high transmission settings must be accompanied by vector control and be prepared to continue for several years

MDA in high transmission settings often found in *P. falciparum* areas of sub-Saharan Africa is more challenging. All but one program failed; the successful program in Uganda[12,36] was sustained for a long duration and accompanied by vector control.

4. **Primaquine has been used in various doses and schedules to target either *P. vivax* hypnozoites or *P. falciparum* gametocytes.**
   Many MDA strategies have administered primaquine alone or in combination with a blood schizonticide, some of which are described in Table 3. This review provides a base on which to build evidence for the most suitable and efficacious drug regimens for MDA.

   More safety data on primaquine regimens are needed. Studies on the safety of primaquine in G6PD replete and deficient populations are currently underway. Reassuringly, a recently completed review of evidence derived from previous studies involving 8-aminoquinolines by the WHO[37] concluded that there is a very low risk of hemolysis among subjects with mild or moderate G6PD deficiency when given a single dose of primaquine. In our review, it was found that primaquine regimens were accompanied by safety monitoring in populations that underwent MPPT (15mg of primaquine daily for 14 days), including in populations that were G6PD deficient. For example, in Azerbaijan, MPPT was given to a population of 30,000 with underlying G6PD rates of 7% (range 0 - 38% depending on village location and ethnicity). Only seven serious adverse events were recorded; nobody required a blood transfusion and all recovered.

5. **Essential components of the delivery strategy**
   Through discussions with key informants, particularly those who actually implemented MDA campaigns in the field, essential parts of the delivery strategy have been identified:

   a. **Directly observed treatment (DOT)**
      All key informants saw DOT as an essential part of a delivery strategy. Of note, DOT using multiple day regimens has been achieved on a large scale.

   b. **Safety monitoring**
      Safety monitoring was built into the DOT regimens for MPPT and supported the early detection of adverse events, followed by cessation of drug therapy in some cases. Monitoring involved the appropriate management of adverse events, including the capacity to provide blood transfusions.

   c. **Coverage (and mobility) monitoring**
      Coverage of greater than 80%, and in the context of MPPT, greater than 90% was repeatedly mentioned as key to success. In successful implementation, delivery systems were equipped to track people who did not receive MDA doses and included a system to find them. Some programs also monitored population mobility. Although not widely discussed in this paper, importation of parasites into a community already cleared of infection is a vital issue to be considered.

   d. **Community participation**
      For sustained impact of MDA alone or in combination with vector control, community participation, understanding and acceptance are essential. Even in the Solomon Islands, where intense efforts were made to educate and engage the community, MDA failed because people were unwilling to take MDA drugs when they were not sick.

Evidence gaps

1. **The most efficacious regimen to use for MDA**
   The appropriate regimen will depend on the parasite species to be targeted and the endemicity setting. Optimizing the MDA regimen may be less important than optimizing the delivery system; however, specific questions should be answered, including the benefits of adding low-dose primaquine for *P. falciparum* or single-dose tafenoquine to ACTs for both *P. falciparum* and *P. vivax*, the addition of other anti-transmission agents such as ivermectin and methylene blue, and the role of new drugs as they become available.[2]

2. **The size of population to target**
   Large populations have been targeted, but in the successful campaigns they were treated as small units. For example, groups of approximately 200-300 people were targeted by delivery teams for MPPT. This seems to be essential for achieving high coverage with DOT and active community participation. In addition, in very low transmission settings, it may be possible to target very few people. For example, in Jiangsu during the 2000s, for every case reported in a health facility, about 30 people (the household of the case and immediate neighbors) were treated with MDA. When targeting smaller populations, fewer resources are required, implementation is simpler, and the intervention is often more readily accepted by the community. Understanding the level of targeting that is needed for effective MDA will improve efficiency and scalability.

3. **Combinations of interventions**
   Combinations of interventions will be needed except in highly seasonal settings where there is a season of absolutely no transmission, such as areas of seasonal *P. vivax* transmission. In other areas, all attempts should be made to minimize vector-human contact. If low season transmission only occurs in a few defined hotspots then vector interventions could be highly targeted. However, particularly in the case of *P. falciparum* elimination from higher transmission areas, vector control should be included as a central part of an MDA strategy. Novel combinations including ivermectin, the insecticide treatment of cows, and the use of vaccines such as RTS,S should be considered.

4. **Timing of MDA**
   The review indicated that the majority of studies had been implemented during the malaria season, yet key informants all reported that when aiming to interrupt transmission and eliminate malaria, MDA should be done at the lowest point of transmission. The timing of delivery also needs to take into consideration local knowledge on population movement. For example, in the Gambia, many farmers travel early during the dry season in order to earn alternative income in other parts of the country, returning just before the rainy season to prepare the fields. MDA scheduled for the beginning of the dry season would thus miss a significant proportion of the community. Determining the best time to deliver MDA should be a priority and may be setting-specific. The development of tools to help programs identify when to implement would be beneficial.

5. **Mobility and importation**
   This review did not address mobility and importation of parasites, but we recognize the importance of reducing the effect of population movement to ensure the sustained success of MDA (see UCSF Global Health Group Background Paper *Effective Responses to Malaria Importation*, 2014).

Recommendations

1. **Spring primaquine-based MDA / MPPT is a widely implemented intervention for seasonal *P. vivax* and appears to be successful in rapidly responding to epidemics**
   Discussions with stakeholders should take place to consider strategies like MPPT for the elimination of *P. vivax*. Alternatively, the use of longer-acting tafenoquine as a single dose may improve compliance.[38,39] Regardless of drug choice, these strategies must include adverse event monitoring.

2. **In moderate and high transmission settings MDA programs should be designed to incorporate intensive vector control and continue for several years**
   A holistic approach to the use of MDA should be taken with a long-term view. MDA strategies must be recurrent and supported by intense vector control, and a post-MDA implementation plan must be established in advance.

3. **Research agenda to address the lessons learned and gaps**

   a. **Efficacy studies for MDA strategies (e.g. drug combinations) should be done in small rapid studies to determine what strategy feeds into the next stage**
      Efficient study designs should be used to rapidly indicate which drug combinations are most efficacious. End points can be measures of transmission such as change in sporozoite rate or parasite prevalence, and do not have to be demonstrations of interruption of transmission. Small differences in efficacy between combinations are likely to be less important than delivery in overall effectiveness.

   b. **Modeling the impact of MDA efficacy and MDA delivery**
      In order to determine the most efficient investments for BMGF, modeling may support the decision whether to focus on MDA drug combination, delivery of that drug or the delivery of a vector control/ MDA combination.

   c. **Large implementation studies should test delivery strategies, combinations of vector control and MDA and be designed for success (e.g. multiple years of intervention with a post-MDA plan)**
      Specific implementation studies should focus on the delivery method (see below for important elements) and include a long-term vision. Vector control should be included, particularly as part of a mop-up phase after a round of MDA. Finally, preparation for the post-MDA phase should be considered and built into the study at the outset.

4. **Focus on small operational units for delivery**
   The elements for successful delivery involve small units for delivery and should contain the following:
   a. Directly observed treatment
   b. Safety monitoring
   c. Coverage and mobility monitoring
   d. High degree of community participation
   e. Operational sustainability where multiple rounds will be needed

5. **More specific terms regarding the large scale use of antimalarial drugs in malaria control and elimination should be defined**
   This review highlights the fact that the term MDA encompasses a broad and disparate collection of strategies. Defining specific terms for the various strategies will lessen confusion and help facilitate the comparison of strategies.

In conclusion, MDA for malaria, especially with regard to seasonal settings of *P. vivax* transmission, should be considered for operational implementation. In higher endemic settings and for *P. falciparum* the importance of combining MDA with vector control and other interventions should be considered from the outset. Delivery of MDA strategies may be a more important factor in achieving impact than the efficacy of an individual MDA regimen. The Bill & Melinda Gates Foundation investments into MDA as a strategy should reflect this value chain.

Appendix A: Mass drug administration for malaria (Cochrane Review)

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008846.pub2/full

Appendix B: 240 studies assessed for inclusion

The 72 studies excluded from this background paper review are in *italics* and the 31 studies assessed as part of the Cochrane Review are in **bold** (note: Paik 1974 was included in the Cochrane Review as two separate studies, bringing the total number of assessed studies to 32)

1 Abraham AC, Samuels RD. Epidemiology of Malaria in the Nizam-sagar Ayacut Area, Niz'amabad District, Hyderabad State. Journal of the Malaria Institute of India 1944; 5: 305–318.

2 Afridi MK, Rahim A. Further Observation on the Interruption of Malaria Transmission with Single Dose of Pyrimethamine (Daraprim). Rivista di Parassitologia 1959; 20: 229–42.

3 Ahorlu CK, Koram KA, Seake-Kwawu A, Weiss MG. Two-year evaluation of Intermittent Preventive Treatment for Children (IPTc) combined with timely home treatment for malaria control in Ghana. Malaria Journal 2011; 10: 127.

4 Ahorlu CK, Koram KA, Seakey AK, et al. Effectiveness of combined intermittent preventive treatment for children and timely home treatment for malaria control. Malaria Journal 2009; 8: 292.

5 Aikins MK, Pickering H, Alonso PL, et al. A malarial control trial using insecticide-treated bed nets and targeted chemoprophylaxis in a rural area of The Gambia, West Africa. 4. Perceptions of the causes of malaria and of its treatment and prevention in the study area. Transactions of the Royal Society of Tropical Medicine and Hygiene 1993; 87: 25–30.

6 Alicata JE, Dajani SW. Observation of Pyrimethamine (Daraprim) as a Suppressant of Malaria in a Small Village in Jordan. American Journal of Tropical Medicine and Hygiene 1955; 4: 1006–8.

7 Aliev S, Saparova N, Aliev S, Saparova N. Current malaria situation and its control in Tadjikistan. Meditsinskaia Parazitologiia i Parazitarnye Bolezni 2001; 35–7.

8 Aliev S. Malaria in the Republic of Tadjikistan. Meditsinskaia Parazitologiia i Parazitarnye Bolezni 2000; 27–9.

9 Allen SJ, Otoo LN, Cooke GA, O'Donnell A, Greenwood BM. Sensitivity of Plasmodium falciparum to Maloprim after five years of targeted chemoprophylaxis in a rural area of The Gambia. Transactions of the Royal Society of Tropical Medicine and Hygiene 1990; 84: 666–7.

10 Alonso PL, Lindsay SW, Armstrong Schellenberg JRM, et al. A malaria control trial using insecticide-treated bed nets and targeted chemoprophylaxis in a rural area of The Gambia, West Africa. 6. The impact of the interventions on mortality and morbidity from malaria. Transactions of the Royal Society of Tropical Medicine and Hygiene 1993; 87: 37–44.

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12 Alving AS, Arnold J, Robinson DH. Mass therapy of subclinical vivax malaria with primaquine. Journal of the American Medical Association 1952; 149: 1558–62.

13 Amangel'diev KA. Current malaria situation in Turkmenistan. Meditsinskaia Parazitologiia i Parazitarnye Bolezni 2001; 37–9.

14 Archambeault CP. Mass Antimalarial Therapy in Veterans Returning from Korea. Journal of the American Medical Association 1954; 154: 1411–5.

15 Archibald H. Field trials of mass administration of antimalarial drugs in Northern Nigeria. World Health Organization 1960; 1–11.

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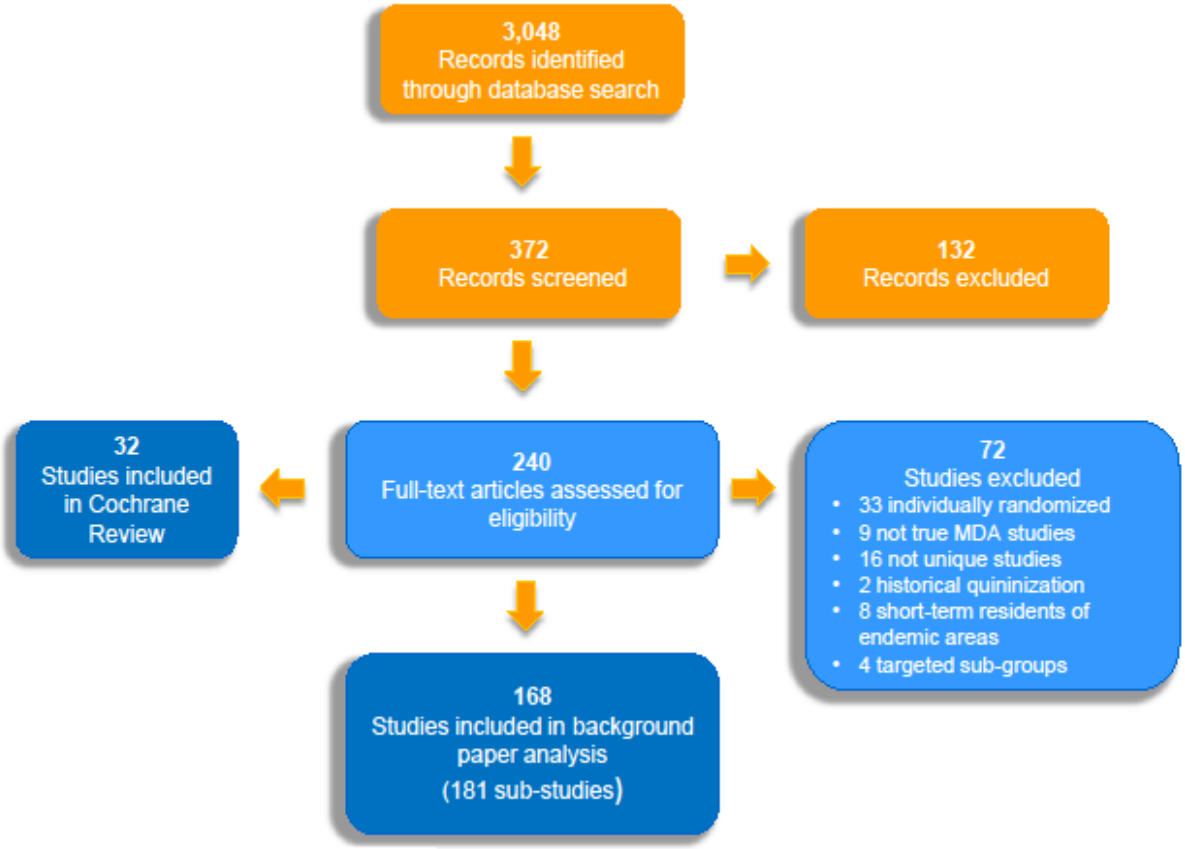
Appendix C: Study exclusion/inclusion process



Appendix D: MDA interview guide

The Malaria Elimination Initiative within the Global Health Group at UCSF is in the process of researching and drafting a background paper about mass drug administration for malaria. The purpose of this paper is to inform future strategy, policy, programming, and research related to MDA, particularly in elimination settings. We are documenting strategies that have already been tried and either succeeded or failed, as well as strategies currently being tested or implemented. We are also interested in ideas on what should be done in the future.

With this in mind, we would like you to tell us about your experiences with and viewpoints on malaria MDA. Please note that we will not use your name or the content of any materials you send to us in our background paper – your responses will be kept confidential and simply serve to improve our understanding of MDA.

1. Please describe your experience with MDA, and if relevant, attach any supporting documentation (protocols, unpublished studies, etc) that you are comfortable sharing with us.
    a. What worked, and why?
    b. What did not work, and why not?

2. If you could design the perfect MDA program, what are your ideal parameters?
    a. Level of endemicity at time of intervention:
    b. Seasonality of intervention (pre-, during, or post-transmission period):
    c. Target population (who, how many, and where):
    d. Drug regimen (which drugs, # of dosages, duration of treatment):
    e. Co-interventions (IRS, ITNs/LLINs, etc):
    f. Method of delivery (Directly Observed Therapy, use of community volunteers, central distribution vs house visits, etc):
    g. Degree of community engagement (how to maintain involvement):
    h. Other parameters:

3. What do you think are the biggest roadblocks to a successful MDA campaign? How would you address them?

4. Do you think MDA should play a role in elimination/eradication efforts? Why or why not?

5. Who else would you recommend we speak to about MDA?

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